



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|------------------------|------------------|
| 10/621,009 | 07/15/2003 | Bob D. Brown | OASBIO.002C2 | 3319 |
| 20995 | 7590 | 01/03/2006 | EXAMINER | |
| KNOBBE MARTENS OLSON & BEAR LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, CA 92614 | | | GOLDBERG, JEANINE ANNE | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1634 | |

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/621,009

Applicant(s)

BROWN, BOB D.

Examiner

Jeanine A. Goldberg

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 December 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 and 50-74 is/are pending in the application.
- 4a) Of the above claim(s) 71-74 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 and 50-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>9/05</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the papers filed June 28, 2005. Currently, claims 1-17, 50-74 are pending. Claims 71-74 have been withdrawn as drawn to non-elected subject matter.
2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.
3. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-2, 4-17, 50-52, 54-70 are rejected under 35 U.S.C. 102(e) as being anticipated by Ulanovsky et al. (US Pat. 6,197,556 B1, filed May 7, 1997).

Ulanovsky et al. (herein referred to as Ulanovsky) teaches modular branched primers. The stem portions of branched primers are constant and bind portions of variable modules together to give specificity to the initial priming (extension) yet allow amplification using conventional primers to proceed (col. 2, lines 23-26). As seen in Figure 2(1)- Figure 2(4), a pair of branched primers are extended in both the forward and reverse directions followed by a pair of unbranched primers. A branched pair of primers is comprised of a front module, a front arm, a back module and a back arm (Figure 4). The two oligonucleotide modules (front and back) also have an "arm segment" which is complementary to a nucleotide sequence site in a template (col.2, lines 43-45). Ulanovsky teaches that "front" refers to the 3' extending (downstream) sequence and "back" refers to the 5' end (upstream). The stem segments are complements of each other and anneal to form the stem of the branched primer (col. 2, lines 30-41). The arm segments is complementary to a nucleotide sequence site in a template to be amplified (col. 2, lines 43-50). The first initial extension strand is annealed to a reverse primer which may be either branched or not to form a second initial extension strand (col. 2, lines 50-55). Then the products are amplified by using amplification primers that include a reverse primer and/or at least one primer homologous to the stem sequence of the first and/or second branched primer (col. 2, lines 55-60). The strand resulting from the extension of the first initial primer is used as a template and the two PCR primers are a reverse primer and the front module of the first initial primer (or a universal primer homologous to the stem of the first module)(col. 9, lines 45-55)(limitations of Claim 8, 10, 17).

Ulanovsky teaches a nucleotide connecting the variable segment with the rest of the oligonucleotide (linkers) can have any base, but preferably such modification, as Inosine or Deoxynebularin (both available from Glen Research Corp., VA, USA), which have approximately equal energy of base-pairing with all four normal bases. This linker between the arm and stem can also be just a chain of atoms (linker) with no base at all, like "AminoModifier II", available for DNA synthesis from Clontech, CA, USA. The purpose of the weak base-pairing of the linker is to make the annealing site more unique. Otherwise, that is if the linker has one of the four normal bases without weakened base-pairing, it can generate undesirable extra binding sites together with nucleotides adjacent to it (limitations of Claim 2, 11).

Ulanovsky also teaches that the arm of each oligonucleotide module sequence preferably contains at least one artificial base to reduce steric hindrance that may be caused by proximity of the stem to the extension point and/or to enhance the annealing stability. These base modifications can be either of bases or backbones in modular primer that improve the stability of annealing, such as PNA, methyl phosphonate, 5-methylcytidine and 2-aminoadenosine (col. 2, lines 60-67; col 13, lines 17-20)(limitations of Claim 5, 6, 14, 15). As seen in the example, the PCR amplification is demonstrated using four branched DNA primers (col. 18)(limitations of Claim 67-68). At least one of the amplification primers is optionally protruding by one or more bases immediately downstream of the 3'-end. This protrusion increases the sequence-specificity of the amplification (col. 4, lines 38-42)(limitations of Claim 4). The protruding amplification primers may include artificial bases, which reduce the number of possible

sequences of these primer that need to be made (col. 4, lines 40-43). Ulanovsky teaches using a thermostable polymers for the initial extension such as ampliTaq and Stoffel fragment (col. 2, lines 55-65). Figure 4 illustrates the first target binding region comprising at least 6 nucleotides, namely 6 nucleotides (limitations of Claim 7, 16). Ulanovsky teaches the present invention also includes a library that is a collection of modular oligonucleotides in separate receptacles (i.e. kit)(col. 4, lines 59-67)(limitations of Claims 50-52, 54-70).

Response to Arguments

The response traverses the rejection. The response asserts that nowhere in Ulanovsky is it disclosed that the branched primers assemble in the absence of the target (see page 11 of response filed December 2, 2005. This argument has been considered but is not convincing because Ulanovsky teaches "in a branched primer the modules are physically linked together, that is they hybridize to each other as well as to the target DNA, thereby forming a 3-way junction (see Figure 4). Thus it is clear from Ulanovsky that the two primers hybridize to each other, i.e. readily associate with each other to form a stem structure in the absence of a target nucleic acid.

It is noted that Ulanovsky does not have to teach that which would be inherent. By looking at the structure of the primers, the length of the stems are such that it the two primers would hybridize. The stem formed is illustrated as 10 contiguous nucleotides that would hybridize to form a structure. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 3, 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulanovsky et al. (US Pat. 6,197,556 B1, filed May 7, 1997) as applied to Claims 30, 35, 47 above and further in view of Stefano et al. (US Pat. 6,287,772, filed April 29, 1998).

Ulanovsky does not specifically teach using a flexible linker of polyethylene glycol, polyethylene, polypropylene, polyesters, between the first stem region and the target binding region.

However, Stefano teaches in Figure 2A a linker between the first stem region and the target binding region. Stefano teaches PNA is a polyamide (col. 7, lines 14-15). Moreover Stefano teaches spacers are used to minimize the adverse effects that bulky labeling reagents might have in hybridization properties of non-nucleic acid probes (col. 7, lines 30-40). Linkers typically induce flexibility and randomness into the probe or otherwise link two or more nucleobase sequences of a probe or component polymer (col. 7, lines 30-40). Stefano teaches that many linker/spacer moieties are known in the art and provides a variety (col. 7).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have added a spacer/linker, as taught by Stefano, into

the primer modules of Ulanovsky for the expected benefit taught by Stefano. Stefano teaches that spacers/linkers are used to minimize adverse effects, increase flexibility and randomness. Thus, the ordinary artisan would have been motivated to incorporate a spacer/linker into the branched probe of Ulanovsky between the arm and the target region to minimize adverse effects, and increase flexibility.

Response to Arguments

The response traverses the rejection. The response asserts that since Ulanovsky does not teach or suggest the branched primers, Stefano does not cure the lacking teachings. This argument has been considered but is not convincing because Ulanovsky does teach and suggest the branched primers assemble in the absence of the target nucleic acid. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

3. **No claims allowable over the art.**
4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

Art Unit: 1634

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Egholm et al. (US Pat. 6,451,588, September 2002) teaches multipartite high-affinity nucleic acid probes which comprise a flexible linker (see Figure 1A).

B) Weston et al. (US Pat. 6,391,593, May 21, 2002) teaches methods of detecting nucleic acid sequences using modified nucleic acid probes (see Figure 1).

C) Kandimalla et al. (US Pat. 6,372,427, April 2002) teaches cooperative oligonucleotides.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Art Unit: 1634

A handwritten signature in black ink, appearing to read "J. Goldberg". The signature is fluid and cursive, with the first letter "J" being particularly large and stylized.

Jeanine Goldberg

Primary Examiner

December 27, 2005